REMARKS

Claims 1-32 are canceled without prejudice, and claim 53 is added. Upon entry of the present amendment, claims 33-53 will be pending in the present application.

Claims 33, 34, and 43 are amended, and new claim 53 added, to clarify the subject matter Applicants regard as their invention. Support for the amendment to claims 33, and 34, in which the phrase "preventing or treating" is replaced with "inhibiting," is found in the specification as filed at page 36, lines 23-25, at page 38, lines 27-29, at page 39, lines 33-37, and at page 40, lines 3-5. Support for new claim 53 is found in the specification as filed at page 7, lines 23-26 and at page 9, lines 34-36. All the amendments to the claims are fully supported by the specification as filed. No new matter has been added.

Also transmitted herewith for filing in connection with the above-identified patent application are corrected formal drawings consisting of twenty-one (21) replacement sheets of drawings for Figures 1A - 7 B. The word "intradermally" was repeatedly misspelled as "intraterminally" in the formal drawings previously filed. The formal drawings submitted herewith correct that mistake. No new matter has been added.

Paragraph 3 of the Office Action

In paragraph 3 at page 1 of the present Office Action, the fourth non-final office action on the merits issued to date in the prosecution of the instant application, the Examiner has, again, withdrawn all previous rejections in view of Applicant's amendment and remarks.

In paragraph 3, the Examiner has stated that it is the Examiner's understanding that the total amount of hsp-peptide complex administered would be between 5 μg and 5000 μg, (claims 16 and 46), more than 100 μg, (claims 17 and 47), and more than 200 μg, (claims 18 and 48). In response, Applicants respectfully disagree. Claims 16 and 46, by virtue of the recitation "is in a range of 5 μg to 5,000 μg," also encompasses the endpoints of the range (as well as points in between). That is, claims 16 and 46 encompass administration of a composition comprising 5 μg of complex as well as administration of a composition comprising 5000 μg of complex. Claims 17 and 47, by virtue of the recitation "100 μg or more" encompass administration of a composition comprising 100 μg of complex or more than 100 μg of complexes, while claims 18 and 48, by virtue of the recitation "200 μg or more" encompass administration of a composition comprising 200 μg of complex or more than 200 μg of complex.

In paragraph 3, the Examiner has also stated that

> Applicant has repeatedly argued that in the context of immunosuppression (which would be used to treat or prevent) graft rejection, heat shock proteins (HSPs) cannot be considered to be interchangeable and that data obtained using one HSP (for example HSP60) cannot be considered to be an indicator of how any other HSP would act in the instant context.

The above statement is not completely accurate. Applicants agree that heat shock proteins are not necessarily predicted or expected to be interchangeable between hsp families in the context of inhibition of graft rejection (in the absence of evidence to the contrary). However, Applicants have argued that heat shock proteins within an hsp family are interchangeable with one another in the context of inhibition of graft rejection, in view of the intrafamily conservation of structure and function. Therefore, for example, in view of Applicants' demonstration that graft rejection can be inhibited by administration of gp96 complexes, it follows that members of the hsp90 family can be used interchangeably in the presently claimed methods. Similarly, in view of the '133 publication which states and provides supporting evidence that BiP, a member of the hsp70 family of heat shock proteins, can be used to inhibit graft rejection (*see e.g.* the '133 publication, at page 5, lines 8-16, page 7, lines 28-30, and at page 22, lines 9-24), it is expected that members of the hsp70 family can be used interchangeably in the presently claimed methods.

The Rejection Under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claim 43 is rejected under 35 U.S.C. § 112, first paragraph as indefinite for being in improper multiply-dependent form. Claim 43, as amended, does not depend upon claim 35, a multiply-dependent claim. Applicants respectfully submit that claim 43, as amended is in proper multiply-dependent form and, accordingly, Applicants respectfully request that the rejection of claim 43 as indefinite under 35 U.S.C. § 112, second paragraph, be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

Claims 1-2, 6-19, 21, and 32-52 are rejected 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. At page 3 of the Office Action the Examiner has stated that although the present specification is enabling for:

> a method for inhibiting the rejection of BALB/cJ skin when transplanted onto a C57BL/6 mouse, said method comprising administering to a

> C57BL/6 mouse gp96 purified from a BALB/cJ source, said administration comprising subcutaneous injection of 100 μg 10 days prior to transplantation, repeated 3 days prior to transplantation,

the Examiner has, nevertheless, alleged that the present specification is not enabling for:

> a method for treating or preventing rejection of a grafted cell, tissue, or organ in a mammal comprising administering to a mammal a composition comprising purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cell, tissue, or organ.

That is, according to the Examiner, the "specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation" for the reasons provided at pages 3-6 of the Office Action.

In particular, the Examiner has noted that "little is known regarding treating or preventing graft rejection by administering HSPs." The Examiner has also noted that, in view of the immunostimulatory activity of hsp-peptide complexes, as disclosed *inter alia* in the '119 patent of Srivastava, the presently-claimed immunosuppressive use of those complexes for the inhibition of graft rejection is a surprising and unexpected result.

In the second full paragraph at page 4 of the present Office Action, the Examiner has asserted that an effective dosage for hsp-peptide complexes to be administered to a human would be at least 60-fold greater than the maximum dose disclosed in the specification as filed, while that to be administered to a horse or cow would be at least 600-fold greater than the maximum dose disclosed in the specification as filed. That is, the Examiner has assumed that an "appropriate" hsp-peptide dosage for a human or other mammal will necessarily be directly proportional to the dose used in a murine model system. Therefore, it appears that the Examiner is attempting to suggest that the specification is not enabling for dosages that the Examiner has assumed should be effective and appropriate. As discussed below, the Examiner's assumptions directly contradict the teaching of the specification and have no reasonable basis. His basis for the rejection is, therefore, unwarranted and improper.

With respect to the scope of the claims, in the first full paragraph at page 4 of the present Office Action, the Examiner has stated that:

> said claims encompass the claimed method employing *all* hsps (except hsp60 and cpn10) which Applicant has repeatedly argued (and demonstrated with sequence alignments) are *not* related and are *not* interchangeable. Clearly then, given the highly unexpected nature of the instant invention, said invention cannot be considered to be enabled for any HSP not demonstrated (in the specification or art) to be immunosuppressive in the instant context (graft rejection).

In the first full paragraph at page 4, the Examiner further alleges that treatment with rat gp96 provided results that were only a little better than those observed in the controls; moreover, the Examiner asserts that "in no case was graft rejection ever 'prevented' as claimed." Accordingly, the Examiner concluded that "not even all gp96's (even those likely to be closely related) can be considered to be enabled."

In reply to the rejection under 35 U.S.C. § 112, first paragraph, Applicants note that "to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the *claimed invention* without 'undue experimentation'." [1] With respect to the manner in which an inventor teaches his or her invention, the United States Court of Customs and Patent Appeals has stated that:

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance ... As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. [2]

The presently-claimed invention is directed toward inhibition of graft rejection by administering compositions comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cells, tissue, or organ, and the hsp is a member of the hsp90 family or a member of the hsp70 family of heat shock proteins.

In paragraphs 9-13 of his Declaration under Rule 132, Dr. Srivastava has presented evidence and reasoning in support of his conclusion that hsp90 family members, such as gp96, and hsp70 family members, such as hsp70, can be used for the inhibition of graft rejection. Dr. Srivastava has noted that the experiments described below demonstrate that gp96 has an immunosuppressive property, and therefore the data discussed are supportive of the utility of gp96 for the inhibition of graft rejection. These experiments (which have been published in Chandawarkar *et al.* (2004) "Immune modulation with high-dose heat shock protein gp96: therapy of murine autoimmune diabetes and encephalomyelitis" *International Immunology* 16(4): 615-624) ("Chandawarkar")) were conducted by Dr. Srivastava or by his

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1 *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (emphasis added).

2 *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (Fed. Cir. 1971)

co-inventor, Dr. Chandawarkar, or by others under their supervision, at the Center for Immunotherapy of Cancer and Infectious Diseases, at the University of Connecticut School of Medicine.

According to Dr. Srivastava, a first experiment demonstrated that gp96 complexes will suppress an immune response directed toward a tumor. In this experiment, BALB/cJ mice were injected, *inter alia*, with either 10 μg of gp96 complexes isolated from Meth A tumor tissue or with a combination of 10 μg of gp96 complexes isolated from Meth A tumor tissue and 90 μg of gp96 complexes isolated from liver. The immunized animals were subsequently challenged by inoculation with live Meth A tumor cells and the growth of the tumor followed for approximately three weeks. Mice immunized with 10 μg of gp96 complexes isolated from Meth A tumor tissue rejected the tumor in four of the five animals tested. However, those mice immunized with the mixture of 10 μg of gp96 complexes isolated from Meth A tumor tissue and 90 μg of gp96 complexes isolated from liver were the same as the buffer control; *i.e.* there was no inhibition of tumor growth (*see e.g.* Fig. 1 of Exhibit B). Thus, according to Dr. Srivastava, administration of a total dose of 100 μg of gp96 complexes (10 μg of gp96 complexes isolated from Meth A tumor tissue and 90 μg of gp96 complexes isolated from liver) appears to have suppressed the anti-tumor immune response that had been observed upon administration of 10 μg of gp96 complexes isolated from Meth A tumor tissue.

According to Dr. Srivastava, a second experiment demonstrated that gp96 complexes will suppress development of diabetes in NOD mice that develop this disease spontaneously. As noted by Dr. Srivastava, administration of 100 μg of gp96 complexes to NOD mice prevented development of diabetes in 60% - 80% of those animals. In addition, Dr. Srivastava noted that these mice remained free of this disease during the entire observation period (*i.e.* for at least six months), as illustrated in Fig. 4(b) of Exhibit B of his Declaration under Rule 132. Moreover, as Dr. Srivastava has indicated, adoptive transfer experiments have established that this suppression of diabetes is mediated by $CD4^+$ T cells (*see e.g.* Exhibit B of Dr. Srivastava's Declaration under Rule 132, at page 619, right column first full paragraph). Dr. Srivastava also pointed out that administration of 10 μg of gp96 complexes did not inhibit development of diabetes. Thus, Dr. Srivastava concluded that administration of 100 μg of gp96 complexes inhibited development of an autoimmune disease, diabetes, in NOD mice. Moreover, as Dr. Srivastava indicated, these results were obtained regardless of the source from which the gp96 complexes were isolated, and the observed immunosuppression apparently is a result of the generation of suppressor

$CD4^+$ T cells that are able to inhibit a wide variety of specific $CD8^+$ T cell - mediated immune responses.

Therefore, according to Dr. Srivastava, these results establish that gp96 complexes have an immunosuppressive activity. Moreover, as pointed out by Dr. Srivastava, the experiments described in the '652 application show that administration of 100 μg and 200 μg of gp96 complexes isolated from liver, effectively inhibited rejection of skin grafts in mice (*see* Examples 1 and 2 of the '652 application). Accordingly, in Dr. Srivastava's judgment, this evidence, taken together with the experiments described above, indicates that gp96 complexes are useful for inhibiting graft rejection. More specifically, according to Dr. Srivastava, these data demonstrate that administration of gp96 complexes will inhibit an immune response directed against foreign tissue (*i.e.* Meth A tumor cells) as well as an autoimmune response directed against self tissue, and will also inhibit the immune response underlying rejection of a graft.

Therefore, in view of the above, Applicants respectfully submit that enablement of the presently-claimed methods is supported by the data of Examples 1 and 2 (as summarized at page 39, lines 32-37 and at page 41, lines 4-19 of the specification as filed, and as depicted in Fig. 1 and Fig. 2), that demonstrate an improved level of graft survival in those animals administered hsp-peptide complexes, particularly those administered 100 μg - 200 μg of a purified population of hsp-peptide complexes isolated from liver. By 10 days post-grafting (Example 1) and by 18 and 22 days post-grafting, (Example 2) there exists a population, albeit a minority, of treated animals that have not rejected their grafts whereas control animals have. Accordingly, these data demonstrate an improved level of graft survival in the treated animals, and even a temporary inhibition of graft rejection is useful and within the scope of the claims.

In this context, Applicants also respectfully request that the Examiner direct his attention to Chandawarkar, which confirms the teaching of the instant specification by demonstrating that a member of the hsp90 family possesses an immunosuppressive activity first disclosed in the present invention. As noted above, this publication, from the present inventors' laboratory, confirms the experimental research disclosed in the present specification, demonstrating immunosuppression of pre-existing immune responses in four different systems. Administration of gp96 complexes suppressed: allergic encephalomyelitis in two different model systems, autoimmune diabetes in the NOD mouse (which mouse is genetically predisposed to the development of diabetes), and immunity to transplanted tumors. Moreover, as noted above by Dr. Srivastava, these effects were seen regardless of

the source of the gp96 complexes administered, *i.e.* whether isolated from normal or tumor tissue (Chandawarkar at page 619, right column, last paragraph).

As discussed in paragraphs 14 and 15 of his Declaration under Rule 132, Dr. Srivastava has indicated that where it has been shown that an activity is mediated by administration of gp96 complexes of one species, it would be obvious that that such gp96 complexes could be substituted with gp96 complexes isolated from any species. This is so because gp96 proteins are very highly conserved among different species, exhibiting, for example, a minimum of 95% amino acid sequence identity among human, rat, and murine gp96 species (Exhibit D of Dr. Srivastava's Declaration under Rule 132).

Dr. Srivastava has also concluded that graft rejection can be inhibited by administration of heat shock protein complexes wherein the heat shock protein is a member of the hsp90 family of heat shock proteins. This is so because (a) members of an hsp family, *e.g.* the hsp90 family, are expected to have very similar activities, even though different members of an hsp family may comprise amino acid sequence variations (*e.g.* epitopes) that may permit immunological distinctions to be made (*see e.g.* Lindquist *et al.* (1988) "The Heat-Shock Proteins" *Annu. Rev. Genet.* 22: 631-77; particularly 634-40; Exhibit I) (Reference BJ), (b) the immunosuppressive effects observed, for example in Chandawarkar (discussed herein and in Dr. Srivastava's Declaration) were not dependent on the tissue used for isolation of the gp96 complexes used (*e.g.* tumor, pancreatic, or liver tissue) indicating that the effects are specific to the hsp *per se*, and (c) members of the hsp90 family of heat shock proteins, including hsp90 and gp96, are highly conserved proteins (Exhibit I of Dr. Srivastava's Declaration under Rule 132, at pages 634-635). For example, as Dr. Srivastava has indicated, there is a minimum of 98% amino acid sequence identity among human, rat, and murine hsp90 species, as well as a minimum of 47% amino acid sequence identity between *e.g.* human gp96 and hsp90 of rat, murine, and human species (Exhibit D of Dr. Srivastava's Declaration under Rule 132). Thus, according to Dr. Srivastava, where one member of a given heat shock protein family has been identified as having a specific activity, such as the ability to inhibit graft rejection, it would be predictable that other members of the same hsp family would have the same activity. Therefore, in view of the disclosure of the '652 application regarding the activity of gp96 complexes in inhibiting graft rejection, Dr. Srivastava concluded that it would be expected that not only would gp96 complexes isolated from different species but also members of the hsp90 family would be interchangeable with one another in the claimed methods.

Therefore in view of the above and in response to the Examiner's rejection, Applicants submit that within a given heat shock protein family, individual members of that family are interchangeable with one another in the instantly-claimed methods (page 8, lines 5-10 and 20-22 of the specification as filed). That is, where a member, *e.g.* gp96, of a heat shock protein family has been shown to inhibit graft rejection, then it follows that hsp complexes comprising another member of the same family, *e.g.* hsp90, will also be useful in the for the inhibition of graft rejection.

Applicants also respectfully submit that, in view of the instant disclosure and the demonstrated inhibition of graft rejection using high levels of gp96 complexes, it would have been apparent to those of ordinary skill in the art that the presently-claimed methods could be performed with gp96 complexes isolated from various sources (*e.g.* human, murine, and rat). This conclusion is based upon the remarkable conservation of amino acid sequence homology seen, for example between human and murine gp96 (96% identity), between human and rat gp96 (95% identity) and between rat and mouse gp96 (97% identity) (Exhibit 1), coupled with the knowledge that structurally similar molecules would be expected to have the same activity (*see In re Brana* 51 F.3d 1560, 1567 (Fed. Cir. 1995)).

Applicants further submit that, in view of the above and in light of Dr. Srivastava's Declaration under Rule 132, it would also have been apparent to those of ordinary skill in the art that the presently-claimed methods could be performed using complexes comprising other members of the hsp90 family, *e.g.* hsp90. This is based upon the conservation of amino acid sequence among members of the hsp90 family (including gp96 and hsp90)[3], the expectation that such structurally similar molecules would have similar activities. *See In re Brana* 51 F.3d 1560, 1567 (Fed. Cir. 1995) *see also* Gething *et al.* (1992) Nature 355: 33-45, at page 41) (Reference AW).

Applicants also note that, in view of the above and in light of Dr. Srivastava's Declaration under Rule 132 regarding the intra-familial conservation of amino acid sequence and protein function observed with heat shock proteins, any unpredictability in the present methods for inhibiting graft rejection would be, at worst, confined to differences between hsp families. However, the teaching of the '133 publication regarding BiP would convince those of ordinary skill in the art that, for example, members of hsp70 family of heat shock proteins would also be interchangeable with one another in the presently-claimed methods. In this

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[3] Human, rat, and mouse hsp90 species each share at least 98% amino acid sequence identity (Exhibit 2), while the amino acid sequence of human gp96 shares 47% identity with that of rat, mouse and human hsp90 species (Exhibit 3).

context, Applicants respectfully request that the Examiner direct his attention to the discussion *infra* of the '133 publication as well as paragraph 16 of the Declaration under 37 C.F.R. § 1.132 of Dr. Srivastava, with respect to the use of hsp70 family members in the presently-claimed methods and the support regarding the use of hsp70 for inhibiting graft rejection that is provided by the '133 publication.

As noted above, the Examiner has indicated that the dosage ranges disclosed and claimed for the use of hsp complexes are too low to be effective. Applicants do not agree with this assertion. As Dr. Srivastava has noted in paragraph 16 of his Declaration under Rule 132, with respect to the use of heat shock protein complexes for *stimulating* an immune response against a non-covalently bound peptide, evidence has shown that the extrapolation of an appropriate dose in humans based upon data obtained in rodents is not directly proportional to their difference in mass. In fact, as indicated for example in U.S. Patent No. 5,837,251, the human dose is approximately the same as that for a mouse, within a factor of fifty. This indication has been demonstrated to be accurate based upon human clinical trials in which clinical responses have been observed upon administration of doses of gp96 complexes of between 2.5 μg and 100 μg (*see e.g.* Exhibit F of Dr. Srivastava's Declaration under Rule 132 (immunization of patients with 25 μg of tumor-derived gp96 complexes) and Exhibit G Dr. Srivastava's Declaration under Rule 132 (immunization of patients with either 5 μg or 50 μg of tumor-derived gp96 complexes)). Moreover, in his Declaration, Dr. Srivastava indicated that he is not aware of any information or any reason that would suggest that this minimal impact of weight upon effective dose would not also be applicable with respect to the effective dose of heat shock protein complexes to be administered for graft rejection. Accordingly, Dr. Srivastava indicated that he is not aware of any reason why the dose ranges disclosed and claimed in the '652 application would not be appropriate for inhibition of graft rejection in humans.

Thus Applicants submit that the Examiner has not established a *prima facie* case against this aspect of the presently-claimed invention, Applicants respectfully request that the Examiner withdraw his assertion that the disclosed and claimed dose ranges are too low to be effective in the presently-claimed methods.

The Examiner characterizes Applicants' submitted experimental data as no better than the control data and suggests that the present methods would not be efficacious, *e.g.*, the Examiner has alleged that prevention of graft rejection has not been demonstrated. Accordingly, Applicants respectfully submit that, at least in pertinent part, the Examiner is

alleging that the claimed invention is inoperable, and therefore, this aspect of the rejection under 35 U.S.C. § 112, first paragraph, is based upon an alleged lack of utility.

According to the Utility Guidelines, the standard for a utility rejection is the same whether under § 101 or § 112 [4]. "Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper" (M.P.E.P. 2107.IV). An examiner should, in the first instance, defer to the statements regarding utility in the specification as being true, especially when supported by evidence in the record:

> For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (*i.e.*, believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate. Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. (M.P.E.P. 2107.01.A.)

In cases in which pharmacological processes are claimed, such as the present application, animal data is particularly relevant in evaluating utility.

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process. (M.P.E.P. 2107.03.III.).

Applicants further submit that the data of Examples 1 and 2 (as summarized at page 39, lines 32-37 and at page 41, lines 4-19 of the specification as filed, and as depicted in Fig. 1 and Fig. 2), indicate that there is an improved level of graft survival in those animals administered hsp-peptide complexes, particularly those administered 100 μg to 200 μg of a purified population of hsp-peptide complexes isolated from liver. Therefore, by 10 days post-grafting (Example 1) and by 18 and 22 days post-grafting, (Example 2) there exists a population, albeit a minority, of treated animals that have not rejected their grafts whereas control animals have. Accordingly, these data demonstrate an improved level of graft

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[4] Federal Register 66 (4), at 1097 (January 5, 2001); Section II.A.

survival in the treated animals, and even a temporary inhibition of graft rejection is useful and within the scope of the claims.

In light of the Examiner's assertions regarding the predictive value of Applicants' data, the Examiner's attention is directed to *Nelson v. Bowler* with respect to threshold requirements for establishing utility using experimental data. In *Nelson*, it was alleged by opponents of the subject patent that utility of the claimed compounds had not been established since data supporting an asserted pharmacological activity had not been obtained using, as an example, a specific experimental protocol generally accepted as providing statistically significant data. In reply, the court stated that "rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." [5] Moreover, as long as there is a reasonable correlation between the data generated using an animal model and the claimed therapeutic application, such data will "almost invariably be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process." (M.P.E.P. 2107.03.III)

The basis for accepting such data as adequate proof of utility was provided by the court *In re Brana*, quoting *In re Kimmel*:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans. [6]

Nonetheless, the Examiner has alleged that since treatment with rat gp96 was only little better than the controls with respect to inhibiting graft rejection, "not even all gp96's (even those closely related) can be considered to be enabled. The most likely conclusion to be drawn form the limited data is that the gp96 must derive from the same genetic source as the graft." This conclusion does not logically follow from the observation cited. Applicants submit that those of ordinary skill in the art would conclude that the same result would be obtained using gp96 complexes isolated from sources other than the graft tissue.

For the reasons provided above and in light of paragraphs 13-15 Dr. Srivastava's Declaration under Rule 132, which have been discussed in detail above, those of ordinary skill in the art would appreciate that not only gp96 complexes from different species, but also different members of the hsp90 family could be used in the presently claimed methods for

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5 *Nelson v. Bowler* 626 F.2d 853, 856 (Fed. Cir. 1980)

6 *In re Brana* 51 F.3d 1560, 1567 (Fed. Cir. 1995).

graft rejection. That is in view of the teaching of the present specification and in view of the fact that *e.g.* human, rat, and murine gp96 are at least 95% identical in their amino acid sequence (Exhibit 1), those of ordinary skill would appreciate that these gp96 species would be interchangeable with one another.

Applicants also note that in Experiment 2, cited by the Examiner, only 10 μg of rat gp96 complex was administered (intradermally), while the two groups of mice exhibiting inhibition of graft rejection were those administered 100 μg and 200 μg, respectively, of murine gp96 complexes subcutaneously (*see* page 41, lines 11-13, and page 40, lines 8-25 of the specification as filed). Accordingly, Applicants respectfully submit that given the differences both in dose and route of administration, it cannot be concluded that the gp96 complexes administered must be derived from the same genetic source for successful inhibition of graft rejection.

As noted above and as discussed in paragraph 13 of Dr. Srivastava's Declaration under Rule 132, Dr. Srivastava has concluded that Applicants' data, as presented in Fig. 1 and Fig 2 (and as summarized at page 39, lines 32-37 and at page 41, lines 4-19 of the specification as filed), demonstrate improved survival of skin grafts in those animals administered a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide as compared to control animals. Applicants therefore submit that there is a reasonable correlation between the claimed methods for inhibiting graft rejection and the data provided. Accordingly, Applicants respectfully submit that the data provided is, at a minimum, sufficient to meet the legally-established threshold for utility.

Moreover, the ability of heat shock protein complexes to suppress an immune response was confirmed in Chandawarkar. This publication disclosed that "high doses of gp96 generates $CD4^+$ T cells that down-regulate a variety of ongoing immune responses" (Chandawarkar, Abstract at page 615), and that "depending on the dose of immunization used, gp96 may elicit an antigen-specific immune response (as shown previously) or down-regulate pre-existing pathological autoimmune responses through the generation of immunoregulatory $CD4^+$ T cells" (Chandawarkar, page 615, right column, first paragraph).

Thus, gp96 complexes from normal and cancer tissue were both capable of suppressing an immune response directed against Meth A tumor cells, as well as the autoimmune responses underlying diabetes and experimental autoimmune encephalomyelitis (Chandawarkar, at page 619, right column, last paragraph, which carries over to page 620).

Accordingly, Chandawarkar confirms not only that administration of gp96 complexes is immunosuppressive but also that immunosuppression is observed where such complexes are isolated from sources that are not genetically identical to the tissue targeted by the immune system, as disclosed in the specification as filed (*see e.g.* page 9, line 34, through page 10, line 2). (*Also see* paragraphs 11-13 of the Declaration under 37 C.F.R. § 1.132 of Dr. Srivastava).

The Examiner has also alleged, for the reasons provided at pages 5 and 6 of the present Office Action, that WO 02/072133 (the " '133 publication") cannot be considered enabling for the use of hsp70 family members in the present claims. Applicants do not agree.

To support this assertion, the Examiner has first alleged that the '133 publication relies upon a highly artificial model system and then he has assumed that the Bip-mediated immunosuppressive methods disclosed in the '133 publication are based solely upon shift from a Th1 profile to a Th2 profile in the T cell population. The Examiner has also cited four references that are alleged to establish that a Th1 to Th2 shift is not necessarily immunoprotective (Pakala *et al.* (1997) *J. Exp. Med.* 186: 299-306 ("Pakala"); McFarland (1996) *Science* 274(5295): 2037 ("McFarland"); Mycko *et al.* (2004) *J. Immunol.* 172: 202-213 ("Mycko"); and Pockley (2001) *Transplantation* 71: 1503-07 ("Pockley")). Therefore, according to the Examiner, since the mechanism he has assumed is allegedly not necessarily immunoprotective according to the cited art, it follows that the immunosuppressive activity of BiP has not been enabled by the '133 publication.

As Dr. Srivastava has discussed in paragraph 16 of his Declaration under Rule 132, the '133 publication discloses that the heat shock protein BiP causes $CD14^+$ cells to release IL-10; stimulates $CD8^+$ cells to proliferate and release IL-10; inhibits the recall antigen response; and activates the expression of an array of anti-inflammatory genes in monocytes, including the migration inhibitory factor (MIF), the soluble TNF receptor II and TIMPs, which are tissue inhibitor matrix metalloproteinases. In particular, the '133 publication also discloses, at page 22, lines 6-24 and in Fig. 9, suppression of the allogeneic response by peripheral blood mononuclear cells (PBMC) when BiP is added at the start of monocyte maturation. This assay is a classic method for measuring the immune response to non-self antigens. Accordingly, these activities of BiP, collectively, are consistent with the conclusion reached in the '133 publication that Bip can be used for inhibiting graft rejection. As Dr. Srivastava has also noted in paragraphs 15 and 16 of his Declaration, once a given member of

a heat shock protein family has been shown to have an activity, it is predictable that the other members of the same heat shock protein family will also have that activity due to intrafamily conservation of structure (*see e.g.* Gething *et al.* (1992) "Protein Folding in the Cell" *Nature* 355: 33-45, esp. page 39, right column through the end of page 40) (Exhibit H). Therefore, since the evidence is supportive of the use of BiP to inhibit graft rejection, the evidence also is supportive of such use of other members of the hsp70 family

Applicants also respectfully submit, in response to the Examiner's objections, that, for the reasons provided below (1) the '133 publication employs model systems that are apparently widely used and relied upon in the art, (2) the evidence provided in support of the immunosuppressive activity of BiP is not limited to *e.g.* an increase in IL-10 production (one characteristic of a Th2 profile), and (3) that the art cited by the examiner, *i.e.* Pakala, McFarland, Mycko, and Pockley, neither individually nor collectively would suggest to those of ordinary skill in the art that the disclosure of the '133 publication does not enable the use of BiP for suppression of immune responses.

For example, Applicants note that, for the reasons provided below, the data of Pakala are confined to results obtained in immunocompromised mice. In view of that fact, Applicants respectfully submit that those of ordinary skill in the art would not evaluate the ability of a treatment to inhibit an immune response using an animal model (*scid* mouse) that, in essence, does not have an immune system. McFarland provides that the biochemical mechanisms underlying autoimmunity are more complex than a simple Th1 to Th2 shift. Applicants respectfully submit that the disclosure of the '133 publication is not limited to "a simple Th1 to Th2 shift," and therefore, does not conflict with the cited teaching of McFarland. Although Mycko discloses the *intracellular* role that hsp70 apparently plays in the processing of intracellular antigens, there is nothing in Mycko concerning the extracellular administration of hsp70. Accordingly, Applicants respectfully submit that Mycko is irrelevant in the present context. Pockley is focused on instances in which an hsp, *i.e.* hsp60, has been hypothesized to be the self-antigen or alloantigen attacked in an immune response. In contrast, the '133 publication indicates that it is directed toward the immunomodulatory properties of BiP (*see e.g.* page 2, lines 4-14 of the '133 publication).

For the reasons provided above (and which are discussed in more detail below), Applicants respectfully submit that each of bases asserted by the Examiner in support of his allegation that the '133 publication is not an enabling reference have been rebutted. Accordingly, Applicants respectfully request that the Examiner withdraw his assertion that

the '133 publication cannot be considered enabling for the presently-claimed use in graft rejection.

More specifically, the Examiner has constructed an argument in which he first asserts that the '133 publication "discloses the use of BiP (a HSP70) only in a highly artificial arthritis model," and then presumes that Applicants' argument is based upon an assumption that

> artificial arthritis and graft rejection are both TH1-mediated, thus a treatment for the artificial arthritis model would be effective as a treatment for graft rejection. The document indicates that BiP has an immunosuppressive effect because it stimulates IL-10 release (page 8) which induces an anti-inflammatory shift towards TH-2 (page 23). This capability of inducing IL-10 release and the subsequent shift towards TH-2 is presumably how BiP might function in inhibiting graft rejection.

The Examiner then further presumes that induction of IL-10 release and the subsequent shift towards TH-2 is the basis by which BiP functions in inhibiting graft rejection. Finally, the Examiner marshals art that is alleged to indicate that the biochemical mechanism underlying the '133 publication, *i.e.* at least that defined by the Examiner, would not be effective. Applicants do not agree with the Examiner's reasoning nor his conclusions.

With respect to the Examiner's characterization of the model systems of the '133 publication as highly artificial, Applicants note that the "adjuvant arthritis" model system, *inter alia*, discussed in the '133 publication appears to be of long standing and "has served as a useful model of progressive inflammation of the joints produced by the immune system" (Cohen (1992), "Autoimmunity to hsp65 and the Immunologic Paradigm," in Advances in Internal Medicine, 37: 295-311 (Mosby - Year Book Inc.; at pages 302-303 under the heading "hsp65 and Autoimmune Arthritis"; reference AO). Moreover, the Examiner's characterization appears to reflect a personal opinion, unsupported by fact or citation to relevant art. Accordingly, Applicants submit that the Examiner has not established a *prima facie* argument to support his assertion the model systems employed in the '133 publication are "highly artificial."

As noted above, the Examiner's attack on the '133 publication is focused on, and essentially limited to, a consideration of induction of IL-10 production and a shift in T-cell mediated cytokine production from a TH-1 profile to a TH-2 profile. By doing so, Applicants note that the Examiner has overlooked all the other information and data provided by the '133 publication, that, collectively, have been put forth in the '133 publication to

enable the teaching of the '133 publication regarding the use of BiP to inhibit graft rejection ('133 publication, at page 5, lines 4-16; and page 7, lines 9-10).

For example, the '133 publication provides that BiP "has a general immunomodulatory property" ('133 publication at page 2, line 5) and that

> BiP causes $CD14^+$ cells to release IL-10; stimulates $CD8^+$ cells to proliferate and release IL-10; inhibits the recall antigen response; and activates the expression of an array of anti-inflammatory genes in monocytes, including the migration inhibitory factor (MIF), the soluble TNF receptor II and TIMPs [tissue inhibitor matrix metalloproteinases] ('133 publication at page 2, lines 21-28)

These activities, which are asserted in the '133 publication in support of the general immunomodulatory properties of BiP, are based upon the data in the Examples provided in the '133 publication (page 15, line 19, through page 24, line 15).

In particular, the '133 publication describes the biochemical effects of BiP in two *in vitro* systems. In the first, the allogeneic response of PBMC to monocytes/dendritic cells was reduced to background levels, when those monocytes were matured in the presence of BiP. In the second the lymphocyte response to the recall antigen PPD (tuberculin purified protein derivative), was diminished in the presence of BiP. According to the '133 publication, these findings indicate that administration of BiP will not only facilitate graft acceptance, it will also suppress autoimmune and inflammatory diseases as well ('133 publication, at page 22, lines 6-29).

More specifically, the Examiner has cited Pakala for the proposition that "induction of IL-10 and a TH2 response ... was highly pathogenic." The Examiner further asserted that Pakala "calls into question the entire concept of a shift toward TH2 as a treatment for TH1 pathologies."

With respect to Pakala, Applicants note that this reference states that:

> Autoimmune diabetes is caused by $CD4^+$, T helper (Th1) cell-mediated apoptosis of insulin producing β cells. We have previously shown that Th2 cells bearing the same T cell receptor (TCR) as the diabetogenic Th1 T cells invade islets in neonatal nonobese diabetic (NOD) mice but fail to cause disease (Pakala, Abstract, at page 299).

However, such Th2 cells "produced intense and generalized pancreatitis and insulitis associated with islet cell necrosis, abscess formation, and subsequent diabetes when transferred into immunocompromised NOD.*scid* mice." (Pakala, Abstract, at page 299, emphasis added). However, the kinetics of induction of diabetes in these

immunocompromised mice were slower than those induced by Th1-like cells and the lesions produced did not resemble those seen in the natural disease (*see* Fig. 1 at page 301, and the first paragraph of the Discussion at page 304 of Pakala). In view of the above, Applicants respectfully submit that the observations of Pakala are, at best, limited to the immunocompromised animals that, in addition, are already genetically predisposed to the development of this autoimmune disease. Moreover, Applicants note that Pakala discloses that their results are observed "only in the absence of diverse αβ-T cell compartment," and that it remains to be seen how "the presence of other T cells affect the in vivo function of Th2." (Pakala, at page 304, right column first full paragraph). In addition, rather than questioning the Th1-Th2 shift paradigm, Pakala states that "[i]t would be of obvious clinical advantage if one could deviate an ongoing inflammatory immune response to a benign Th2 response." (Pakala, at page 304, right column, second full paragraph).

Accordingly, Applicants respectfully submit that those of ordinary skill in the art would not rely on data obtained in such a highly artificial system to "call into question the entire concept of a shift toward TH2 as a treatment for TH1 pathologies."

The Examiner also relies upon McFarland, for the assertion that "[m]echanisms of autoimmunity [and presumably graft rejection] are more complicated than a simple TH1-TH2 dichotomy." Applicants do not necessarily dispute this assertion. In fact it is apparent that the named inventors of the '133 publication were also aware of the biochemical complexity involved. That is, the '133 publication does not rely solely upon an assertion of a "TH1 to TH2 shift," as the Examiner has suggested. As noted above, the '133 publication indicates, *inter alia*, that BiP not only causes $CD14^+$ cells to release IL-10, but it also stimulates $CD8^+$ cells to proliferate and release IL-10, inhibits the recall antigen response, and activates the expression of an array of anti-inflammatory genes in monocytes, including the migration inhibitory factor (MIF), the soluble TNF receptor II and tissue inhibitor matrix metalloproteinases ('133 publication at page 2, lines 21-28).

The Examiner has also cited Mycko, alleging that this reference provides another example of "enhancement of another TH1 mediated disease by over-expression of HSP70 and increased Class II presentation of an autoantigen."

In response, Applicants note that this publication was directed toward elucidation of the role played by hsp70 in the "presentation of the major putative autoantigen in multiple sclerosis" (Abstract at page 202). Based upon their data, the authors of Mycko concluded that "hsp70 may modulate MBP [myelin basic protein] processing within the MHC class II

presentation pathway." (Discussion, first paragraph at page 210). Although Mycko suggests that increased levels of intracellular expression of hsp70 may increase the efficiency of antigen processing and, ultimately, antigen presentation as part of the MHC II pathway, there is nothing in this publication regarding administration of hsp70 much less the stimulation of a Th 1 mediated disease by administration of hsp70. Accordingly, Applicants respectfully submit that Mycko is not germane to the purpose for which it was cited; *i.e.* the determination as to whether or not the '133 publication is an enabling reference.

The Examiner has also cited Pockley for the proposition that the "role of heat shock proteins in allograft immunity is unclear and more insight into the processes by which heat shock proteins encounter and are recognized by the recipient immune system after transplantation is required."

In response, Applicants note that Pockley discusses both the well-known intracellular protective role of heat shock proteins, the expression of which is induced by physiological stress (*see e.g.* Gething, cited above), as well as assertions regarding heat shock proteins as targets of the immune response in autoimmune disease and graft rejection. It is the consideration of these roles (one factual and the other alleged) that underlies the alleged "balance between protective and damaging effects" of heat shock proteins in connection with graft rejection referred to by the Examiner.

Applicants respectfully submit, therefore, that the Examiner's statement that Pockley "serves to define the invention of the instant claims as being unpredictable" is in fact, not correct. That is, Pockley is only relevant with respect to a method in which down-regulation of an autoimmune response to a self-hsp is alleged to be useful for delay of graft rejection.

To illustrate the distinction between the alleged methods of delaying graft rejection discussed in Pockley and the present invention, Applicants respectfully direct the Examiner's attention to the specification as filed which discloses that

> Because the protection is based on the immunoregulatory role of the hsp itself (and not its antigenicity), the effectiveness of the treatment is general -- unlike free peptide or other specific graft alloantigen approaches (including where the hsp itself is an alloantigen), the treatment is not limited to a specific target alloantigen of the rejection process (page 3, line 31 to page 4, line 1, of the specification as filed; emphasis added).

Thus, Applicants respectfully submit that the hsp-epitope specific methods for delaying graft rejection focused upon by Pockley are also not germane to the claimed

methods of the instant invention nor those put forth in the '133 publication, which relate to the general immunosuppressive properties of heat shock protein complexes.

In light of all of the above, Applicants respectfully submit that the specification as filed provides those of ordinary skill in the art with sufficient guidance with respect to the choice of heat shock protein complexes that could be used in the presently-claimed methods. In addition, the present specification has disclosed not only the appropriate doses of hsp complex to be administered, but also the various routes and timing for administration of those heat shock protein complexes which will be effective for inhibiting graft rejection (*see e.g.* page 32, line 4 through page 33, line 4, page 37, lines 10-12, and at page 36, lines 26-30 of the specification as filed). Accordingly, Applicants respectfully submit that the information, guidance and experimental detail provided in the present specification are sufficient to enable those of ordinary skill to practice the full scope of the presently-claimed invention without undue experimentation.

Consequently, in light of the teaching and the experimental data provided by the instant specification, Applicants submit that the claimed methods have utility and are fully enabled, and, further, that one of ordinary skill in the art would reasonably predict, at a minimum, that the presently claimed methods would more likely than not be efficacious for the inhibition of graft rejection.

The Rejection of Claims 34-39 and 42-51 Under 35 U.S.C. § 112 First Paragraph Should be Withdrawn

Independent claim 34, as well as claims 35-39 and 42-51 dependent thereon, are rejected under 35 U.S.C. § 112, first paragraph for an alleged lack of written description. More specifically, in paragraph 9, at page 6 of the Office Action, the Examiner has stated that the limitation "wherein the heat shock protein is a member of the hsp70 family of heat shock proteins," which is recited in claim 34, is not supported by the specification as filed.

In response, Applicants respectfully direct the Examiner's attention to page 8 of the specification as filed which discloses, in lines 7-8, that hsp "families have been called hsp60, hsp70, and hsp90" and, at lines 20-22 that "[i]t is contemplated that hsp/stress proteins belonging to all of these three families can be used in the practice of the instant invention." Applicants, therefore submit that the recited limitation is fully supported by the specification as filed, and, accordingly, respectfully request that the rejection of claims 34-39 and 42-51 under 35 U.S.C. § 112, first paragraph for an alleged lack of written description, be withdrawn.

The rejection of claims 1, 2, 6-19, 21, and 32 under 35 U.S.C. § 112 first paragraph is now moot since these claims are now canceled. In view of all of the above, Applicants respectfully submit that there is full support in the present specification which is enabling over the full scope the invention as it is presently claimed, and that claim 43, as amended is not indefinite. Accordingly, Applicants respectfully request that the rejection of claim 43 under 35 U.S.C. § 112 second paragraph, and the rejection of claims 1, 2, 6-19, 21, and 32-52 under 35 U.S.C. § 112 first paragraph be withdrawn.

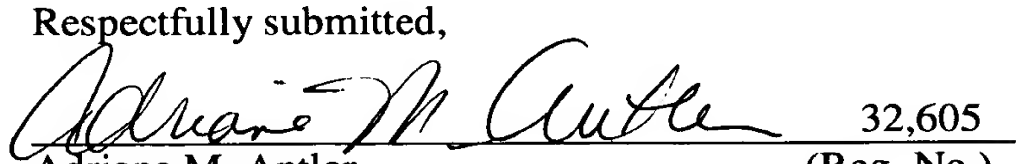
Conclusion

Applicants believe that each ground of rejection of the pending claims has been successfully overcome or obviated. Accordingly, Applicants respectfully request that the rejection of claims 1-2, 6-19, 21, and 32-52 under 35 U.S.C. § 112, be withdrawn.

Applicants submit that the entire application is now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

Date: August 25, 2004



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